"FORMULATION, DEVELOPMENT AND EVALUATION OF NANOCARRIER BASED TOPICAL APPLICATION FOR THE TREATMENT OF DIABETIC WOUNDS"

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1. ABSTRACT OF PROPOSED WORK PLAN/ PROBLEM:

Diabetes mellitus (DM) is a common endocrine disease characterized by a state of hyper-glycemia. DM and its complications can lead to diabetic foot ulcer (DFU). DFU is associated with impaired wound healing, due to inappropriate cellular and cytokines response, infection, poor vascularization, and neuropathy. Effective therapeutic strategies for the management of impaired wound could be attained through a better insight of molecular mechanism and pathophysiology of diabetic wound healing. The conventional treatment for wound healing only focuses on antimicrobial activity but they do not involve inflammation of wound, formation of reactive oxygen species and re-epithelization of wound. So, to overcome these gaps of conventional formulation novel nanocarrier system like liposome, niosome, phytosome, erythrocytes, microspheres, pharmacosomes, solid lipid nanoparticle, nano-structured lipid carrier, etc. are used. Nanocarriers are ideal for topical delivery of drugs in a sustained manner, eliciting cell-to-cell interactions, cell proliferation, vascularization, cell signalling, and elaboration of biomolecules necessary for effective wound healing. The aim of proposed research work is to formulate, develop and evaluate cubosomes based hydrogel (cubosomal nanogel). Cubosomes are nanostructured liquid crystalline particles, made of certain amphiphilic lipids in definite proportions, known as biocompatible carriers in drug delivery. They have unique properties such as thermodynamic stability, bioadhesion, the ability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances, and the potential for controlled release through functionalization. Cubosomes are regarded as promising nanocarrier for topical routes of administration. Cubosomal nanocarrier prepared by high pressure homogenization technique or probe ultrasonication or automated sonication or special technique such as top down or bottom up etc. Cubosomal hydrogel formulation will be formulated, developed optimized and evaluated on basis of various physicochemical parameter like particle size, SEM, TEM, DSC, FTIR, Zeta potential, entrapment efficiency, drug content, in-vitro and in vivo study and stability studies.

Keywords: cubosomes, hydrogel**,** nanoparticle, nanocarrier, diabetes mellitus, wound healing, diabetic foot ulcer, bioadhesion etc.

2. INTRODUCTION:

Diabetes mellitus (DM) is a chronic health problem that is prevalent among the human population. DM is an endocrine disorder which is distinguished by the state of hyperglycaemia (higher level of glucose in the blood), and is classified into Type 1 DM and Type 2 DM. Factors associated with a steady increase in DM are aging populations, dietetic revolutions, and sedentary lifestyles. Based on 2019 prevalence data from the International Diabetes Federation (IDF), the estimated number of adults (20–79) with DM worldwide is 463 million, which is expected to increase to 578.4 million by 2030 and 700.2 million by 2045. It is anticipated that DM may increase in developing countries as compared to developed countries.

DM increases the risk of infection and delays wound healing due to impairment of metabolic activity. As DM advances, a complication that may occur is diabetic wound i.e., diabetic foot ulcers (DFUs), a chronic wound that affects the lifestyle of patients and consequently, heightening the risk of mortality. Though DFU is preventable, it puts a massive burden on patients and health care services. The common primary causes for DFU are poor glycemic control, calluses formation, improper foot care, mainly peripheral neuropathy, angiopathy, poor blood circulation and dryness in skin etc.

The foot ulcer is defined as a full-thickness wound below the ankle in a diabetic patient, irrespective of duration according to the international consensus on diabetic foot. The DFU is a multifactorial pathophysiological state characterized by infection, deep tissues damaged and ulcer. It is a result of combination of many risk factors including foot deformities, peripheral neuropathy, arterial insufficiency, peripheral vascular disease, and trauma. Usually, the DFU develops in three stages. The initial stage is the development of a callus, results from neuropathy. The motor neuropathy causes physical deformity of the foot, and sensory neuropathy leads to ongoing trauma. In sensory neuropathy, skin breakdown occurs due to which microbial growth takes place resulting reoccurrence and delay wound healing. Dry skin because of autonomic neuropathy is also another causative factor. Hence, Regular trauma of the callus causes subcutaneous haemorrhage and ultimately it turned into an ulcer. Severe atherosclerosis of the small blood vessels in the legs and feet, leads to vascular compromise. The abnormalities in endothelial function and extended inflammatory response can affect

microcirculation, may increase basement membrane thickness or capillary thickness, increased blood coagulation, improper blood flow which is another cause of DFU.

New drug-delivery systems (DDSs) may enhance the current and future therapies for these challenging clinical problems. Recently, nanotechnology has become one of the most focused research areas for the treatment of DM patients and its associated complications. The advantage of nanomaterials (with a range of 1–100 nm) are versatility in use, controlled size, and tunability of physiochemical properties. Nanomaterials with a larger surface area to volume ratio allow for cell adhesion, and possibly can encapsulate a greater number of surface functionalized active components to accelerate specific regenerative functions. The nanotechnology-based wound healing methods confer advantages such as topical drug delivery, cell specificity, and sustainable and controlled release of encapsulated drugs for a required period until the wound heals. In the case of wound healing, nanoparticles are ideal for topical delivery, supporting better interactions with the biological target and increased penetration at the wound sites. Besides, encapsulated drugs could be delivered in a sustained manner and delivery rate could be suitably altered by changing the nanoparticle distribution. Thus, wound healing treatments incorporating the nanotherapeutics approach for delivery of therapeutic approach for delivery of therapeutic biomolecules, paves the way for an excellent opportunity to tackle the complexity of diabetic wound healing by. Conceptually, topical delivery of nanotherapeutics has major advantages for chronic wounds such as diabetic wound, by promoting effective wound healing and skin regeneration due to: (a) multifactorial factors and cell-type specificity and (b) use of therapeutic agent for a limited time or until the wound has healed.

Nanotechnology-based materials act as smart nanomaterials in the form of nanofibers and hydrogel, foams loaded with nanoparticles which can encapsulate antibiotics, growth factors, peptides, nucleic acids and extracellular substrates, with the possibility of combined delivery of two different therapeutic agent with dissimilar characteristics to enhance the healing process, that include liposomes, niosomes, pharmacosomes, ethosomes, sphingosomes, transferosomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures, and nanohydrogel etc. Among these cubosomes nanocarriers is the promising carrier for topical drug delivery system in the treatment of diabetic wound healing.

Cubosomes are distinct, nano-structured, sub-micron size particles of bi-continuous cubic structures having two internal aqueous channel and which is being divided by a surfactant-controlled lipid bilayer. It can enclose both hydrophilic, hydrophobic, and amphiphilic active substances. The hydrophilic drugs are enclosed in the hydrophilic vesicles whereas hydrophobic drugs are partitioned between hydrophilic domains. The composition of cubosomes includes lipid, polymer, and surfactant. The structure of cubosomes is dependent on the concentration and shape of the amphiphiles being used and the physiochemical parameters such as pH, temperature, and pressure. The size ranges from 100-500nm having honeycomb like structure.

Components of cubosomes nanocarrier Drug Delivery System:

Amphiphilic lipids: Glyceryl monostearate, Phytantriol etc

Surfactants/Stabilizers: Poloxamer, Poloxamine, Bile salts, proteins, polysaccharide polymers, vitamins etc.

Advantages of cubosomes:

- Improved thermodynamic stability.
- Maximum drug loading capacity because of increased surface area.
- Encapsulate hydrophilic, lipophilic, and amphiphilic drugs.
- Biodegradable lipid imparting bioadhesive and biocompatible properties.
- Administered by different ways of routes.
- Sustained, targeted, and controlled drug release achieved.
- Very simple method of preparation.
- Bi-continuous cubic liquid crystalline phase of cubosomes even stable in excess water.
- These are an excellent vehicle to protect the sensitive drug such as peptides and proteins, from the enzymatic degradation and *in vivo* degradation.

3. REVIEW OF LITERATURE:

1. **Iman M Alfagih *et al*. (2021)** have done a work on Indomethacin loaded cubosomes to improve the dissolution for oral delivery. Glyceryl monooleate based Indomethacin loaded cubosomes dispersion was prepared by using Taguchi design to study the effect of Indomethacin to the disperse phase ratio and poloxamer 407 concentrations on the particle size and entrapment efficiency (%EE). The prepared Indomethacin cubosomes dispersions were in the nanoscale (184.53±0.7 to 261.33±0.8 nm) with reasonable %EE (49.30±2.6 to 95.55±3.4

2. **Adrianna C *et al*. (2020)** did a work on the delivery of Doxorubicin (DOX) loaded cubosomes which demonstrated that several properties make cubosomes a promising alternative in the development of controlled release systems for drug delivery.

3. Yasser M *et al*. (2019) developed Telmisartan (TEL) loaded cubosomes. Four distinctive formulae were selected according to the results of three estimated responses. The liquid cubosomes were successfully adsorbed onto aerosil 380 to form granules. Results revealed that the highest Entrapment efficiency was shown in formulae C5 (59.68 ± 1.3). All the prepared formulae had particle size less than 500nm with PDI < 0.5 and the highest zeta potential results were observed in C5, C7, C9, C11 and C12 (>30 mv).

4. Madheswaran T *et al*. (2019) developed positively charged Liquid Crystalline Nanoparticles (LCN) coated with chitosan (CHI) to enhance the skin permeation and distribution of 5α-reductase inhibitors for the treatment of androgenetic alopecia by ultrasonication method. *In vitro* and *in vivo* skin permeation and retention were studied using porcine abdominal skin and mice skin using the Franz diffusion cell.

5. Yuanfeng Wei *et al*. (2019) described Vinpocetine (VPT) loaded cubosomes with surface cross linked chitosan were prepared by the high-pressure homogenization method. Particle size and zeta potential of chito-cubosomes were determined to be 250nm and +35.9 mV respectively. The results suggested that chito-cubosomes could be a promising drug carrier for enhancing oral absorption with sustained release behaviour.

6. Yanliang Fan *et al*. (2019) formulated and evaluated cubosomes loaded Cefpodoxime Proxetil (CFP) into the Lyotropic Liquid Crystalline Nanoparticles (LLCNs) was investigated to improve their taste. Pluronic F127 was added to improve the colloidal stability of CFP-LLCNs. The optimized CFP-LLCNs showed the particle size of 187.29± 4.12 nm and the encapsulation efficiency of 85.80%. Study showed the prepared CFP-LLCNs were able to reduce the dosing frequency by 24 h sustained release.

7. Badie HA *et al*. (2018) formulated and evaluated Resveratrol loaded LCNPs fabrication and optimization for transdermal delivery was assessed via a quality by design approach based on 23 full factorial designs. Based on the factorial design, the independent operating variables significantly affected the five dependent responses. The cubosomes and hexosomes hydrodynamic diameters were in the nanometre range (135- 256 nm) with narrow particle size distribution, high negative zeta potential ≥ -27.9 mV and entrapment efficiency ≥ 73.5%.

8. Fahima Hashem *et al*. (2018) did a work on cubosomes containing Rebamipide (REB) for improvement of oral absorption. The mean relative bioavailability of the REB loaed cubosomes compared to the drug powder and commercially available tablets (Mucosta®) was 267.67% and 166.29% respectively. The prepared cubosomes significantly improved the in-vivo absorption of REB in comparison with the drug powder and commercially available tablets (Mucosta®)

9. Salwa Salah *et al*. (2017) developed the Etodolac-loaded cubosomes for Rheumatoid arthritis which showed particle size values ranging from 135.95 to 288.35nm and zeta potential values ranging from -18.40 to -36.10 mV. All the cubosomes showed drug loading capacity ranging from 1.28 to 6.09%. The *in vitro* drug release studies revealed a drug release rate up to 15.08%/h. Increasing poloxamer concentration in Etodolac-loaded cubosomes resulted in nanoparticles with less particle size and faster drug release.

10. Liling Mei *et al*. (2017) formulated and evaluated stable self-assembly Cubosome Precursor-Microparticles (CPMs) enhancing dissolution of insoluble drugs, innovative CPMs spray dried from an aqua-free precursor solution was developed to improve cubosome stability. The CPMs disintegration and cubosome self-assembly were demonstrated by the notable morphology variation and the distinct microparticle size decrease from CPMs (10~20 μm) to self-assembly (SA)-cubosomes (150~200 nm).

4. NEED FOR THE STUDY:

Diabetes mellitus (DM) is a serious, chronic, and complex illness characterized by hyperglycemia that resulted from the pancreatic β-cells generate deficient insulin (a hormone that adjusts blood glucose) when the body cannot efficiently custom the insulin or both leads to long-term health consequences. DM and its complications can lead to diabetic wounds specifically diabetic foot ulcer (DFU). DFU is associated with impaired wound healing, due to inappropriate cellular and cytokines response, infection, poor vascularization, and neuropathy. It is estimated that impaired healing of diabetic wounds affects approximately 25% of all patients with diabetes mellitus, often resulting in lower limb amputation, with subsequent high economic and psychosocial costs.

Diabetic wounds are one of the serious, non-healing, chronic health issues faced by individuals suffering from diabetic mellitus. The distinct phases of wound healing are either prolonged or obstructed, resulting in the improper healing of diabetic wounds.

Approximately 15–30% of diabetic patients suffer from diabetic wounds, which is expected to increase annually. The major challenges in treating diabetic wounds are associated with wound infections, alterations to inflammatory responses, angiogenesis, and lack of extracellular matrix (ECM) components. Furthermore, the lack of targeted therapy and efficient wound dressings for diabetic wounds often results in extended hospitalization and limb amputations. Hence, it is essential to develop and improve diabetic wounds specific therapies.

Nanomaterial-based innovative approaches have tremendous potential for preventing and treating wound infections of bacterial origin. They have greater benefits compared to traditional wound dressing approaches.

The present study will focus on formulation of Nanomedicines that are ideal for topical delivery of drugs in a sustained manner, eliciting cell-to-cell interactions, cell proliferation, vascularization, cell signalling, and elaboration of biomolecules necessary for effective wound healing. Also, hey have some attractive and unique properties such as thermodynamic stability, bioadhesion, the ability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances, and the potential for controlled release through functionalization.

5. OBJECTIVES OF RESEARCH/ PROPOSED HYPOTHESIS:

Hypothesis:

Nanomedicine for topical delivery of drugs increased the sustained release of drug, eliciting cell-to-cell interactions, cell proliferation, vascularization, cell signalling, and elaboration of biomolecules necessary for effective diabetic wound healing treatment. Development of biocompatible nanostructured liquid crystalline carrier in the effective treatment of diabetic wounds due to unique properties such as thermodynamic stability, bioadhesion, the ability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances, and the potential for controlled release through functionalization.

Aim: Formulation, Development and Evaluation of Nanocarrier Based Topical Application for the Treatment of Diabetic Wounds.

Objectives of the research work:

- To formulate and develop cubosomes nanocarrier system by using suitable method.
- To characterized and optimized formulated nanocarriers.
- To perform in- vitro drug release of optimized nanocarrier.
- To formulate & evaluate topical dosage form of optimized cubosomes nanocarrier.
- To perform In-vitro study of topical formulation.
- To evaluate In-vivo study of topical formulation.
- To perform stability studies of optimized topical formulation.

5. PLAN OF WORK

1. Literature review
2. Selection and Collection of drug & excipients:
3. Experimental work

    A. Preformulation study:

    a) Spectroscopic studies

    b) Solubility studies

    c) Crystallinity studies

    B. Compatibility studies

4. Formulation development and optimization of cubosomal nanocarrier using suitable method.
5. Characterization of cubosomal nanocarrier system:

    a) Percentage yield and drug content

    b) Particle size and zeta potential

    c) Percentage Encapsulation efficiency

    d) Surface morphology by Transmission electron microscopy (TEM)

    e) Fourier transform infrared spectroscopy (FTIR)

    f) XRD study

    g) Differential scanning colorimetry (DSC)

    h) In vitro drug release study

6. Formulation & evaluation of topical dosage form of optimized cubosomes nanocarrier.
7. In vitro & In-vivo study of topical dosage form.
8. Stability studies as per ICH guidelines.

6. MATERIALS AND METHODOLOGY:

1. **Literature survey:** Literature review and review of research articles.
2. **Selection and Collection of drug & excipients:**

   Drug: Antidiabetic or Antimicrobials or Antibiotics or Antioxidants or Growth factors or herbal plant extract

   Excipients: Amphiphilic lipids (glyceryl mono-oleate, phytantriol), Surfactants, Stabilizers
3. **Experimental work:** Preformulation study and Compatibility study.
4. **Formulation development**

   Preparation of cubosomes nanocarrier: Drug loaded cubosomes nanocarriers will be prepared by one of the following suitable methods:

   a. Melt Dispersion Emulsifying Method
   b. Ultra Sonication Method
   c. Spray Drying Method
   d. Solvent Evaporation Method
   e. Top-down Method
   f. Bottom-up Method
   g. Hydrotrope Method

- Optimization of cubosomes nanocarrier using suitable method.

5. **Characterization of cubosomal nanocarrier system**

   a) Yield and drug content
   b) Particle size and zeta potential
   c) Encapsulation efficiency
   d) Surface morphology by Transmission electron microscopy (TEM)
   e) Fourier transform infrared spectroscopy (FTIR)
   f) XRD study
   g) Differential scanning colorimetry (DSC)
   h) In vitro drug release

6. **Formulation & evaluation of topical dosage form of optimized nanocarriers.**
7. **In vitro & In-vivo study of topical dosage form.**
8. **Stability studies as per ICH guidelines.**

7. Importance of study/ Society application:

International status: Diabetes is a metabolic disorder that ranks as one of the top ten reasons for death among the global population. The International Diabetes Federation (IDF) has reported 463 million diabetic cases in 2019, and this count is suspected to grow to 578 million in 2030. Diabetes mellitus (DM) occurs when the pancreas fails to secrete the necessary amount of insulin required to maintain a normal blood sugar level in the human body.

As a result, the world requires rapid recovery from diabetic wounds to avoid other diabetic complications or keep people with diabetes alive. Various treatments with various approaches have been developed to treat diabetic wounds. Drug delivery through nanoparticle based diabetic wound healing treatments shows some benefits in reducing side effects or quick wound healing. Nanoparticles act as drug delivery systems with controlled drug release. It has already been well demonstrated that nanoparticles treat damaged tissues by stimulating cell proliferation, migration, microbe inhibition, thereby controlling wound healing. Therefore, it is likely that nanotechnology-based remedies will possibly be the next frontier poised for breakthroughs in meeting the clinical needs of chronic wound healing.

United States patent US11369664B2 2022-06-28 Eleos Pharmaceuticals Inc.: Topical composition for improved healing of open wounds

United States patent US2019070266: Treatment diabetic foot ulcers

National status: According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79-year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world." According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps.

As a result, the India requires rapid recovery from diabetic wounds to avoid other diabetic complications or keep people with diabetes alive. Various treatments with various approaches have been developed to treat diabetic wounds. Drug delivery through nanoparticle /nanomaterials-based diabetic wound healing treatments shows some benefits in reducing side effects or quick wound healing.

Significance of the study:

Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. DM and its complications can lead to diabetic foot ulcer (DFU). DFU is associated with impaired wound healing, due to inappropriate cellular and cytokines response, infection, poor vascularization, and neuropathy. Effective therapeutic strategies for the management of impaired wound could be attained through a better insight of molecular mechanism and pathophysiology of diabetic wound healing. Nanoparticles are smaller in size and have high surface area to volume ratio that increases the likelihood of biological interaction and penetration at wound site. They are ideal for topical delivery of drugs in a sustained manner, eliciting cell-to-cell interactions, cell proliferation, vascularization, cell signalling, and elaboration of biomolecules necessary for effective wound healing.

Cubosomes are nanostructured liquid crystalline particles, made of certain amphiphilic lipids in definite proportions, known as biocompatible carriers in drug delivery. Owing to unique properties such as thermodynamic stability, bioadhesion, the ability of encapsulating hydrophilic, hydrophobic, and amphiphilic substances, and the potential for controlled release through functionalization, cubosomes are regarded as promising nanocarrier for topical routes of drug administration. Hence it is need of hour to develop a topical formulation to treat diabetic wound by using cubosomes nanocarrier system.

8. PROPOSED WORK PLAN/ FORMULATION AND STRUCTURE OF STUDY:

Year-wise Plan of work and targets to be achieved:

Sr. No.	Expected target to be achieved	1-6 months	7-10 months	11-22 months	22--27 months	28- 33 months	34-36 Month
01	Literature survey	Literature survey					
02	Selection and collection of drug and excipients	Selection and collection of drug and excipients					
03	Formulation, development and optimization of CNs & topical dosage form	Formulation, development and optimization of Cubosomal nanocarrier and topical dosage form					
04	Evaluation of CNs & topical dosage form	Evaluation of Cubosomal nanocarrier and topical dosage form					
05	In vitro and in vivo study	In vitro and in vivo study and Stability study					
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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Date:

Place:

Research Student **Research Guide**

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